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The Iodomethylation of Nicotine. An Unusual Example of Competitive Nitrogen Alkylation[1]

Jeffrey I. Seeman* and Jerry F. Whidby

Philip Morris Research Center, P.O. Box 26583, Richmond, Virginia 23261

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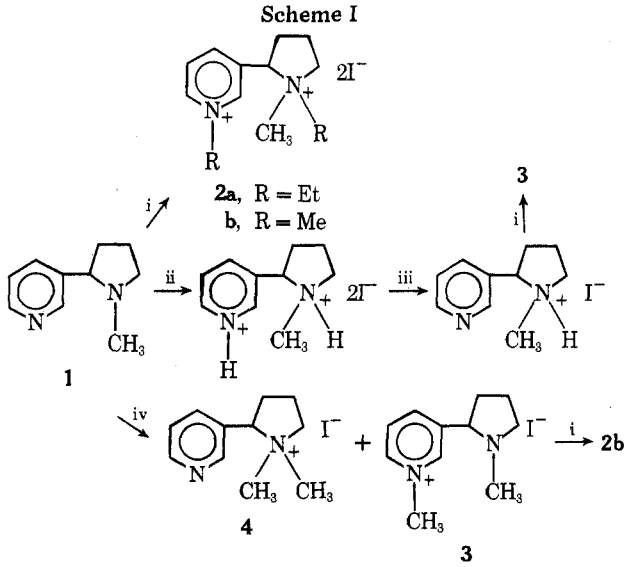
Alkylation of nicotine with 1 equiv of iodomethane in either methanol or acetonitrile leads to ca. 2.5:1 mixtures of *N'*-methylnicotinium iodide (**4**) and *N*-methylnicotinium iodide (**3**), and not to only **4** as previously indicated in the literature. The alkylation results reflect kinetic control of product. Control experiments indicate that the products are formed irreversibly under the reaction conditions. Alkylation of the nicotine analogue *N,N*-dimethyl-3-aminomethylpyridine with 1 equiv of iodomethane led only to trimethyl-3-picolylammonium iodide. Competitive alkylation experiments between nicotine and pyridine and *N*-methylpyrrolidine indicate that alkylation on nicotine's pyrrolidine nitrogen is decelerated, and the causes for this anomalous example of competitive nitrogen alkylation are discussed.

Nicotine (**1**) and its nitrogen alkylated products (e.g., **2–4**) have been of considerable biological and chemical interest for many years.[2-4] The earliest reported work on the alkylation of nicotine was published in 1853 by Kekule[5a] and in 1854 by Stahlschmidt[5b] who treated the alkaloid with iodoethane and iodomethane and obtained nicotine diethiodide (**2a**) and dimethiodide (**2b**), respectively. In 1897, Pictet and Genequand[6] reported their preparation of the two monomethiodides of nicotine, *N*-methylnicotinium iodide (**3**) and *N'*-methylnicotinium iodide (**4**), as shown in Scheme I. It is of interest to

Scheme I



Reagents: i, excess CH_3I; ii, HI; iii, 1 equiv of nicotine; iv, 1 equiv of CH_3I.

note that recent investigators[7] have reported the preparation of these compounds, in some cases with much difficulty, following the old literature procedures.

As a part of our interest in nicotine structure[8] and reactivity,[9] we now report that alkylation of this alkaloid with 1 equiv of iodomethane in either methanol or acetonitrile, following the literature procedures,[6,7c] leads to ca. 2.5:1 mixtures of **4**:**3** and not to only **4** as previously reported[6,7] (see Figures 1–3).[10] However, we have isolated **4** (68%) uncontaminated with either nicotine or **3** by continuous extraction of the aqueous solution of the **3** + **4** mixture with chloroform followed by removal of water from the aqueous phase. Rotary evaporation of the chloroform phase followed by ether trituration led to the isolation of **3** (28%). Alternatively, treatment of an acetic acid solution[11] of nicotine with 2 equiv of iodomethane at room temperature for 3 days followed by removal of the acetic acid and trituration with ether yields (58%) pure **3**.

The identity of these compounds is evident from their ^1H NMR spectra (see Figures 1–3 and data cited in the Experimental Section), elemental analyses, and mode of synthesis. In addition, treatment of either **3** or **4** with iodomethane leads quantitatively to *N,N'*-dimethylnicotinium diiodide (**2b**). Thus, simple high-yield procedures for the preparation of the two nicotine monomethiodides, uncontaminated with each other, are now available.

The Menschutkin reaction has been shown to be reversible in some cases, generally under forcing conditions.[13] Treatment of pure **3** or a 4:1 mixture of **4**:**3** at 120 °C in acetonitrile in a sealed, degassed NMR tube resulted in no discernible chemical change after 36 h as judged by ^1H NMR of the total reaction mixture. Thus, the reaction product ratios in the nicotine alkylations are not complicated by the potential equilibration of products and starting material following selective quaternization; i.e., the alkylation results reflect kinetic rather than thermodynamic product control.

The iodomethylation of nicotine at pH >6 is an unusual example of competitive nitrogen quaternization,[13,14] especially since the pyrrolidine nitrogen of nicotine is almost three orders of magnitude more basic than nicotine's pyridine nitrogen (see Table I). While many factors other than basicity have a kinetic influence on the Menschutkin reaction, e.g., steric hindrance and solvation,[15] two limiting conditions could explain the nicotine alkylation results: (1) a rate decrease in pyrrolidine alkylation caused by the pyridine ring; and (2) a pyridine nitrogen alkylation rate enhancement due to the presence of the pyrrolidine ring. In an effort to distinguish between these two possibilities, two competitive alkylation experiments were performed. Treatment of a 1:1 mixture of nicotine and *N*-methylpyrrolidine with 1 equiv of iodomethane in methanol resulted in the formation of only *N,N*-dimethylpyrrolidinium

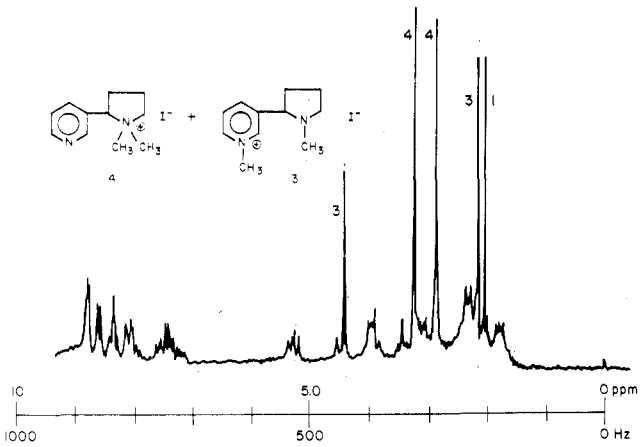


Figure 1. NMR spectra of total crude reaction product of nicotine and 0.75 equiv of iodomethane in acetonitrile in the presence of sodium carbonate at 100 MHz. The singlets are the *N*-methyl groups of nicotine, **3**, and **4**.

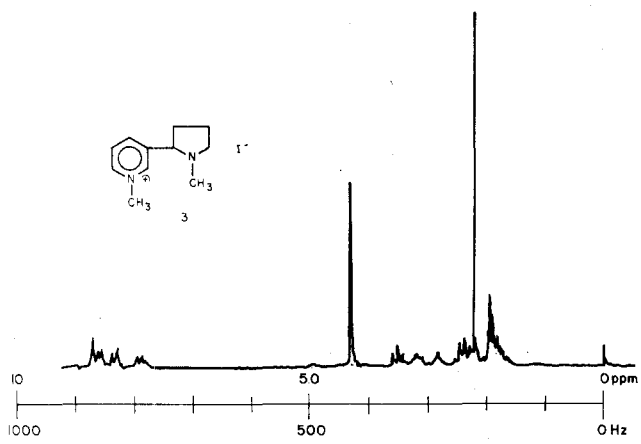
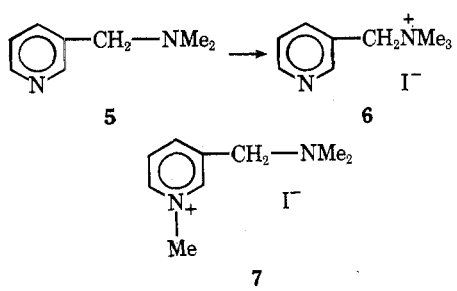


Figure 2. NMR spectra of *N*-methylnicotinium iodide (**3**) in acetonitrile-d_3 at 100 MHz.

iodide; no nicotine methiodides were observed (<1%) in the ^{1}H NMR spectra of the crude reaction product. Similarly, treatment of a 1:1 mixture of nicotine and pyridine with 1 equiv of iodomethane in acetonitrile led to a mixture of pyridine methiodide:**3**:**4** (ca. 1:1:2.5). It appears that for nicotine, alternative 1 above is operative and 2 above is not.

The pK_{a_1} value of nicotine (pK_{a_1} = 7.84, pK_{a_2} = 3.04)[9,16a] is 2.34 pH units less than the pK_a of *N*-methylpyrrolidine (pK_a = 10.18)[16b] and 1,2-dimethylpyrrolidine (pK_a = 10.2)[9] and 1.43 pH units less than that of 1-methyl-2-phenylpyrrolidine (pK_a = 9.27).[9,16] It is likely that this decrease in basicity of nicotine's pyrrolidine nitrogen will manifest itself in a decrease in this nitrogen's nucleophilicity. However, the pK_a values of nicotine compare extremely well with those of the nicotine analogue *N*,*N*-dimethyl-3-aminomethylpyridine (**5**) (pK_{a_1} = 7.8, pK_{a_2} = 3.1).[9] Alkylation of **5** with 1 equiv of iodomethane in acetonitrile results only in the formation of **6**;



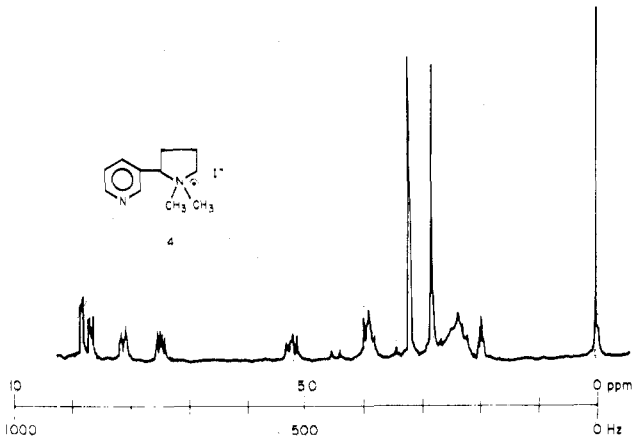


Figure 3. NMR spectra of *N*′-methylnicotinium iodide (**4**) in acetonitrile-d_3 at 100 MHz.

Table I. pK_a Values of Nicotine and Selected Nicotine Analogues

Compd	pK_{a_1}	pK_{a_2}	Ref
Nicotine (**1**)	7.84	3.04	*a*, *b*
1-Methyl-2-phenylpyrrolidine	9.27		*a*, *b*
N-Methylpyrrolidine	10.18		*c*
1,2-Dimethylpyrrolidine	10.2		*a*
N,*N*-Dimethyl-3-aminomethylpyridine (**5**)	7.8	3.1	*a*
Pyridine	5.19		*b*

[a] Reference 9. [b] Reference 16a. [c] Reference 16b.

no **7** was detected by evaluation of the ^{1}H NMR of the crude reaction mixture. Thus, a correlation between basicity and nucleophilicity alone does not account for the entire deceleration observed for nicotine. See Table I.

There are numerous examples of steric control in the Menschutkin reaction,[18] and the presence of the pyridine ring appears to act by destabilizing the N′-iodomethylation transition state for nicotine. Additional electronic or stereoelectronic factors can also be cited as important controlling factors. Experiments in progress may serve to elucidate the importance of these features.

Finally, it is interesting to note that the difficulty reported by many investigators in crystallizing **4** from the reaction of nicotine with iodomethane[7] stems from contamination with the now established major impurity, coalkylation product *N*-methylnicotinium iodide (**3**). In addition, the purity of the "*N*′-methylnicotinium iodide" obtained by the old literature methods[6] is open to question.

Experimental Section

The ^{1}H NMR spectra were obtained on a Varian XL-100 NMR spectrometer equipped with a Digilab NMR-3 FT accessory. The ir spectra were obtained on a Perkin-Elmer 621 spectrophotometer using Nujol mulls. Uv spectra were obtained on a Beckman spectrophotometer Acta-CV.

Iodomethylation of Nicotine in Acetonitrile. *N*′-Methylnicotinium Iodide (4) and *N*-Methylnicotinium Iodide (3). To a solution of 20.0 g of freshly distilled nicotine (0.123 mol) in 150 ml of acetonitrile was added sodium carbonate (9.75 g, 0.092 mol).[10] To this rapidly stirred mixture was added iodomethane (13.1 g, 0.0192 mol) (*Caution*: Cancer suspect agent!) in 150 ml of acetonitrile. The reaction mixture was stirred at room temperature for 3 days and filtered, and the precipitate washed with additional acetonitrile. The precipitate was tested for iodide by the standard silver nitrate–nitric acid method and no iodide was indicated. The filtrate and the washes were combined and rotary evaporated, yielding a thick, tan oil. NMR analysis of this oil showed it to be a mixture of nicotine:**4**:**3** (see Figures

1–3). This mixture was dissolved in 60 ml of water and continuously extracted with chloroform for 3 days. The combined chloroform portions were dried ($MgSO_4$) and rotary evaporated yielding an oily solid which was triturated with anhydrous ether. The resulting tan solid was vacuum dried, yielding 7.9 g (28% yield based on iodomethane used) of *N*-methylnicotinium iodide (**3**) identical with that prepared as described below.

The aqueous phase from the continuous extraction was rotary evaporated yielding a thick, yellow oil which was extremely hygroscopic. This material was subjected to high vacuum pumping for 1 week and spontaneously crystallized, giving 19.2 g (68% yield based on iodomethane used) of *N'*-methylnicotinium iodide (**4**): mp 135–137 °C; NMR (CD_3CN) δ 2.78 (s, 3), 3.16 (s, 3), 3.88 (m, 2), 5.10 (dd, 2, J = 8.1, 6.2 Hz), 7.52 (dd, 1, J = 8, 2 Hz), 8.10 (dt, 1, J = 8, 2, 2 Hz), 8.76 (dd, 1, J = 5, 2 Hz), and 8.86 (d, 1, J = 2 Hz); ir (Nujol mull) 3445 (m), 3000 (m), 1594 (m), 1579 (m), 1432 (vs), 1418 (m), 1333 (m), 1254 (m), 1027 (m), 1008 (m), 957 (m), 880 (m), 813 (s), and 718 cm^{-1} (vs); uv[19] max (H_2O) 264.5 nm (ε 2320), 258 (3140), 252 (2990), 226.0 (15 370).

Anal. Calcd for $C_{11}H_{17}N_2I$: C, 43.43; H, 5.63; N, 9.21; I, 41.72. Found: C, 43.35, 43.27; H, 5.50, 5.49; N, 9.12, 9.18; I, 42.13, 42.20.

N'-Methylnicotinium iodide was treated with 2 equiv of picric acid in absolute EtOH. The precipitate was crystallized from the reaction medium, yielding bright yellow crystals: mp 159–162 °C; NMR (Me_2SO-d_6) δ 2.78 (s, 3), 3.09 (s, 3), 3.77 (m, 2), 4.99 (m, 1), 7.99 (dd, 1, J = 8, 3.6 Hz), 8.56 (s, 4, picrate), 8.97 (dd, 1, J = 8, 1.6 Hz), and 9.03 (d, 1, J = 1.6 Hz).

Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.58, 43.53; H, 3.69, 3.71; N, 17.45, 17.50.

***N*-Methylnicotinium Iodide (3).** Freshly distilled nicotine (20.0 g, 0.123 mol) was added cautiously to 130 ml of glacial acetic acid. The mixture was allowed to cool to room temperature, and iodomethane (35.0 g, 0.246 mol) (*Caution*: Cancer suspect agent!) was added all at once. The resulting solution was allowed to stand at room temperature for 3 days. Most of the acetic acid was removed by rotary evaporation with mild heating. Trituration with ether (vigorous shaking) led to the formation of a nicely crystalline mass which was filtered and washed with ether to remove residual acetic acid and unreacted nicotine. The precipitate (25.7 g) was treated with concentrated aqueous sodium carbonate until the resulting solution reached a pH ≃7. This solution was rotary evaporated under mild heating to a dryness and heated under reflux with 400 ml of chloroform for 2 h. The mixture was allowed to cool to room temperature and filtered. The residue was reextracted with chloroform under reflux, following the procedure above, and the combined chloroform layers were dried ($MgSO_4$), filtered, rotary evaporated, and crystallized from acetone yielding 21.3 g (58%) of analytically pure **3**: mp 165–165.5 °C (lit.[6] 165 °C); NMR (CD_3CN) δ 2.26 (s, 3), 2.92 (m, 1), 3.28 (m, 1), 3.59 (m, 1), 4.42 (s, 3), 8.02 (br m, 1), 8.5 (br d, 1, J = 8 Hz), 8.76 (br d, 1, J = 6 Hz), and 8.88 (br s, 1); ir (Nujol mull) 3027 (m), 2775 (vs), 1635 (m), 1503 (s), 1290 (m), 1190 (m), 1162 (s), 1153 (m), 1049 (s), 906 (m), 899 (m), 811 (s), and 671 cm^{-1} (vs); uv[19] max (H_2O) 264 nm (ε 4620), 224 (14 500).

Anal. Calcd for $C_{11}H_{17}N_2I$: c, 43.43; H, 5.64; N, 9.21; I, 41.72. Found: C, 43.62; H, 5.66; N, 9.15; I, 41.97.

The filtrate from the above reaction could be re-treated with additional quantities of iodomethane, thereby increasing the yield of **3**.

Competitive Alkylation Experiments. To a solution of nicotine (32.4 mg, 0.2 mmol) in ca. 200 μl of acetonitrile-d_3 in a 5-mm NMR tube was added pyridine (15.8 mg, 0.2 mmol) followed by iodomethane (28.4 mg, 12.5 μl, 0.2 mmol). The resulting solution was allowed to stand at room temperature in the presence of ca. 5 mg of sodium carbonate overnight. NMR analysis of the solution indicated that the NMR resonance of the *N*-methyl group of pyridine methiodide overlapped the resonance of the *N*-methyl group of *N*-methylnicotinium iodide (**3**). This equivalency was destroyed by addition of a small volume of trifluoroacetic acid, protonating **3** and shifting its *N*-methyl group downfield by ca. 2.5 Hz. The ratio of **3**:**4**:pyridine methiodide was ca. 1:2.5:1.

To a solution of nicotine (30.8 mg, 0.19 mmol) in ca. 200 μl of methanol-d_4 in a 5-mm NMR tube was added *N*-methylpyrrolidine (16.4 mg, 0.19 mmol) followed by iodomethane (27.2 mg, 11.9 μl, 0.19 mmol). The solution was allowed to stand at room temperature overnight in the presence of ca. 5 mg of sodium carbonate. NMR analysis of the resulting solution indicated only the formation of *N,N*-dimethylpyrrolidinium iodide: NMR (methanol-d_4) δ 3.12 (s, 6), 3.50 (m, 4), and 2.30 (m, 4). Neither **3** nor **4** (<2%) was observed in the reaction mixture.

Alkylation of *N,N*-Dimethyl-3-aminomethylpyridine (5). To a solution of *N,N*-dimethyl-3-aminomethylpyridine (139 mg, 0.98 mmol) in ca. 5 ml of acetonitrile was added iodomethane (62.3 μl, 0.98 mmol). The resulting solution was allowed to stand at room temperature overnight. NMR analysis indicated only the formation of the trimethylammonium iodide **6**: mp 128–130 °C (lit.[17] 135 °C); NMR (acetonitrile-d_3) δ 3.28 (s, 9), 4.94 (s, 2), 7.56 (dd, 1, J = 8, 4.5 Hz), 8.16 (dt, 1, J = 8, 2, 2 Hz), 8.72 (dd, 1, J = 4.5, 2 Hz), and 8.92 (d, 1, J = 2 Hz).

Anal. Calcd for $C_9H_{15}N_2I$: C, 38.86; H, 5.44; N, 10.07; I, 45.63. Found: C, 38.73; H, 5.54; N, 9.92; I, 45.84.

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Registry No.—**1**, 54-11-5; **3**, 21446-46-8; **4**, 5959-86-4; 4 picrate, 60282-17-9; **5**, 2055-21-2; **6**, 60306-32-3; iodomethane, 74-88-4; *N,N*-dimethylpyrrolidinium iodide, 872-44-6.

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(10) (a) The alkylation of nicotine with iodomethane in acetonitrile was performed in the presence of sodium carbonate to exclude the possibility of the formation of small amounts of HI which would protonate the more basic pyrrolidine nitrogen of nicotine, thereby causing pyridine alkylation (cf. nicotine alkylation in acetic acid). Identical results were observed, however, in the absence of sodium carbonate. (b) The reaction of **5** with iodomethane in acetonitrile led only to **6** in spite of the *absence* of sodium carbonate.
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